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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	7

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Application No.	Applicant(s)
09/284,009	LEWIS ET AL
Examiner	**Art Unit**
Eleanor Sorbello	1633

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-50* is/are pending in the application.

4a) Of the above claim(s) *1-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)

16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s).

18)☐ Interview Summary (PTO-413) Paper No(s).

19)☐ Notice of Informal Patent Application (PTO-152)

20)☐ Other

Response to amendment

1. Applicant's amendment and response to the official Office Action mailed July 07, 2000 as Paper No. 5, has been received and filed on October 12, 2000 as Paper No. 6B. Claims 1-24 has been canceled, and claims 25-50 have been added. Claims 25-50 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's argument.

2. Applicant's arguments are addressed below on a per section basis. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 25-41 and 45-50 are rejected under 35 USC § 112, first paragraph for the same reasons of record.

Newly added claims 25-41 and 45-50 are directed to (1) therapeutic compositions comprising any hypoxia and/or ischaemic and/or stress regulatable agent, and a binding agent that binds to a cell surface element of a mononuclear phagocyte comprising a gene; (ii) delivery systems for targeting aforementioned therapeutic compositions and (iii) methods for targeting desired agents to sites or (iv) methods for treating conditions associated with hypoxic, ischaemic or stress sites *in vivo* and therefore fall in the realm of gene therapy. The scope of the newly added claims are not changed necessarily. Applicant's arguments have been fully considered but they are

Applicants argue that the gene may encode a prodrug activation enzyme or regulate the expression of a suicide gene and cite pages in the specification where the aforementioned were referred to. However, as mentioned above, the scope of the claims still fall in the realm of gene therapy. Being a new field with experimental methods not established as routine and the lack of predictability in the art, detailed guidance for the preparation of therapeutic compositions, quantities required for delivery, site of delivery etc. must be stated specifically with supporting examples *in vivo* for the disclosure to be enabled. Applicants rebut examiner's arguments that the invention is sufficiently exemplified for methods of *in vivo* and ex vivo gene delivery/gene transfer and cite the specification wherein these methods have been described. However, examiner contends that the examples cited were *in vitro* examples of gene transfer to cell lines in cell culture. Due to the unpredictability in the art these *in vitro* examples cannot be extrapolated to that which will take place *in vivo* without undue experimentation. Claims 31-33 are directed to a therapeutic compositions comprising a binding agent such as any viral vector, an adenoviral vector or a lentiviral vector. However as stated in the FOAM, the specification does not specifically describe the administration of any viral vector to an art accepted model except by prophetic consideration. Due to the unpredictability in the art of administering viral vectors, details of the specific viral vector with specific quantities, specific compositions and sites of delivery are required to be stated. The results from one viral vector cannot be randomly extrapolated to result in that expected from any viral vector

based on certain criteria such as if the disease is inherited requiring sustained expression or short term expression etc. Examiner acknowledges that Example 5 demonstrates the effect of clamp induced hypoxia on macrophage infiltration into tumor xenographts which led to increased infiltration of macrophages. Examiner also acknowledges that mononuclear phagocytes may be used to deliver drugs to hypoxic/ischaemic sites where mononuclear phagocytes are typically present. However, applicant's disclosure fails to support the claimed invention whereby drugs or prodrugs such as genes encoding a prodrug are delivered in therapeutic compositions resulting in therapy.

Claim 39 claims an inducible or repressible promoter. However there is no support in the specification for enablement of either an inducible or repressible promoter. Due to the nature of the invention, state of the art, unpredictability in the art and undue experimentation required to make and use the invention as claimed, the claim is rejected for reasons explained in the FOAM and as argued herein.

4. Claims 42-44 are rejected under 35 U.S.C. 112 first paragraph for the same reasons of record. Claims 42-44 replaced claims 19-20, but the context of the claims are not changed necessarily and therefore stand rejected. Claim 44 is directed to a method of selectively destroying mononuclear phagocytes. The specification however does not provide enablement for such.

5. Claim 44 is rejected under 35 U.S.C. 112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

Claim 44 is directed to a method and is rejected as being incomplete for omitting essential active steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: (I) How is the cytotoxic agent which is regulated by hypoxia or ischaemia or stress, attached?; and (2) What is the step that has to be performed which will eventually result in the destruction of the mononuclear phagocytes?

6. Claim 42 is objected to as it recites the following phrase: " stress regulatable gent". This phrase should be amended to read: " stress regulatable agent".

7. Claims 25-50 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Ratcliffe et al. in view of Leek et al. and further in view of Ferkol for the following reasons.

The therapeutic composition claims, namely claims 25-41, 49 and 50 are directed to compositions, because the therapeutic language recited in the claims does not impart any particular or new feature. This is therefore interpreted as an "intended use". The composition has no other components other than the components of the vector and a pharmaceutically or therapeutically acceptable carrier. Plasmid vectors are routinely stored in buffers that would be pharmaceutically acceptable. Therefore, this is considered an obvious feature.

Ratcliffe et al. taught nucleic acid constructs comprising hypoxia response elements operably linked to a coding sequence of a gene encoding a pro-drug activation system. Ratcliffe also taught the importance of including tissue-specific

inducible expression control sequences, nucleic acid constructs comprising such sequences and their use for selective targeting for anti-cancer therapy. (see col. 1 paragraphs 1 and 2). Ratcliffe additionally taught the administration of retroviruses comprising the pro drug of interest by direct injection into the affected site.

Ratcliffe et al. did not teach regulatable agents and binding agents that bind/target mononuclear phagocytes.

Leek et al. taught increased macrophage infiltration into tumors such as invasive breast carcinoma and that this cell type may represent an important target for therapy in breast cancer. (See abstract).

Ferkol et al. taught that receptor-mediated gene transfer has been shown to be successful in introducing transgenes into cells. They taught that this procedure involved linking the DNA to a polycationic protein usually poly-L-lysine containing a covalently attached ligand, which is selected to target a specific receptor on the surface of the tissue of interest. (See col. 1 lines 25-30). Ferkol et al. also taught the tissue specificity of mannosylated DNA complex in targeting DNA to macrophages, which are large scavenger cells or phagocytes. (See col. 5 lines 5-9).

Hence one of skill in the art would have been motivated to combine the teachings of Ratcliffe et al. with that of Leek et al. and Ferkol et al. to result in the instant invention.

Therefore it would have been *prima facie* obvious at the time the invention was made to combine the teachings of Ratcliffe, Leek and Ferkol to make nucleic acid constructs comprising hypoxia responsive elements and a binding agent that binds to a

the art would have been motivated to modify the non-targeting constructs, responsive to hypoxia responsive elements and include a specific ligand or sequence, enabling it to target a specific cell type such as macrophages which migrate to a specified location such as a tumor. The aspect of delivering the construct in a composition that could be a common buffer or even water, is well known in the art and does not require undue experimentation. One of ordinary skill in the art would have reasonably expected success because the field of molecular biology is relatively advanced in that modifying constructs with sequences that fulfill a desired end result would not require undue experimentation.

Conclusion

8. Claims 25-50 stand rejected.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication should be directed to Eleanor Sorbello, who can be reached at (703)-308-6043. The examiner can normally be reached on Mondays-Fridays from 6.30 a.m. to 3.00 p.m. EST.

Questions of formal matters can be directed to the patent analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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